○ G. *Habeas Corpus/ 2255* ☐ 530 Habeas Corpus-General ☐ 510 Motion/Vacate Sentence	○ H. *Employment Discrimination* ☐ 442 Civil Rights-Employment (criteria: race, gender/sex, national origin, discrimination, disability age, religion, retaliation) *(If pro se, select this deck)*	○ I. *FOIA/PRIVACY ACT* ☐ 895 Freedom of Information Act ☐ 890 Other Statutory Actions (if Privacy Act) *(If pro se, select this deck)*	○ J. *Student Loan* ☐ 152 Recovery of Defaulted Student Loans (excluding veterans)
○ K. *Labor/ERISA (non-employment)* ☐ 710 Fair Labor Standards Act ☐ 720 Labor/Mgmt. Relations ☐ 730 Labor/Mgmt. Reporting & Disclosure Act ☐ 740 Labor Railway Act ☐ 790 Other Labor Litigation ☐ 791 Empl. Ret. Inc. Security Act	○ L. *Other Civil Rights (non-employment)* ☐ 441 Voting (if not Voting Rights Act) ☐ 443 Housing/Accommodations ☐ 444 Welfare ☐ 440 Other Civil Rights ☐ 445 American w/Disabilities-Employment ☐ 446 Americans w/Disabilities-Other	○ M. *Contract* ☐ 110 Insurance ☐ 120 Marine ☐ 130 Miller Act ☐ 140 Negotiable Instrument ☐ 150 Recovery of Overpayment & Enforcement of Judgment ☐ 153 Recovery of Overpayment of Veteran's Benefits ☐ 160 Stockholder's Suits ☐ 190 Other Contracts ☐ 195 Contract Product Liability ☐ 196 Franchise	○ N. *Three-Judge Court* ☐ 441 Civil Rights-Voting (if Voting Rights Act)

V. ORIGIN

● 1 Original Proceeding ○ 2 Removed from State Court ○ 3 Remanded from Appellate Court ○ 4 Reinstated or Reopened ○ 5 Transferred from another district (specify) ○ 6 Multi district Litigation ○ 7 Appeal to District Judge from Mag. Judge

VI. CAUSE OF ACTION (CITE THE U.S. CIVIL STATUTE UNDER WHICH YOU ARE FILING AND WRITE A BRIEF STATEMENT OF CAUSE.)

15 U.S.C. Section 154(b)(4) – review of determination of patent term adjustment

VII. REQUESTED IN COMPLAINT ☐ CHECK IF THIS IS A CLASS ACTION UNDER F.R.C.P. 23 **DEMAND $** _____ Check YES only if demanded in complaint **JURY DEMAND:** YES ☐ NO ☒

VIII. RELATED CASE(S) IF ANY (See instruction) YES ☐ NO ☒ If yes, please complete related case form.

DATE November 26, 2008 **SIGNATURE OF ATTORNEY OF RECORD** Christopher J. Kelly

INSTRUCTIONS FOR COMPLETING CIVIL COVER SHEET JS-44
Authority for Civil Cover Sheet

The JS-44 civil cover sheet and the information contained herein neither replaces nor supplements the filings and service of pleadings or other papers as required by law, except as provided by local rules of court. This form, approved by the Judicial Conference of the United States in September 1974, is required for the use of the Clerk of Court for the purpose of initiating the civil docket sheet. Consequently a civil cover sheet is submitted to the Clerk of Court for each civil complaint filed. Listed below are tips for completing the civil cover sheet. These tips coincide with the Roman Numerals on the Cover Sheet.

I. COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF/DEFENDANT (b) County of residence: Use 11001 to indicate plaintiff is resident of Washington, D.C.; 88888 if plaintiff is resident of the United States but not of Washington, D.C., and 99999 if plaintiff is outside the United States.

III. CITIZENSHIP OF PRINCIPAL PARTIES: This section is completed only if diversity of citizenship was selected as the Basis of Jurisdiction under Section II.

IV. CASE ASSIGNMENT AND NATURE OF SUIT: The assignment of a judge to your case will depend on the category you select that best represents the primary cause of action found in your complaint. You may select only one category. You must also select one corresponding nature of suit found under the category of case.

VI. CAUSE OF ACTION: Cite the US Civil Statute under which you are filing and write a brief statement of the primary cause.

VIII. RELATED CASES, IF ANY: If you indicated that there is a related case, you must complete a related case form, which may be obtained from the Clerk's Office.

Because of the need for accurate and complete information, you should ensure the accuracy of the information provided prior to signing the form.

CIVIL COVER SHEET

JS-44
(Rev.1/05 DC)

I (a) PLAINTIFFS	DEFENDANTS
Solvay Pharmaceuticals GMBH	Hon. Jon W. Dudas, Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office
(b) COUNTY OF RESIDENCE OF FIRST LISTED PLAINTIFF (EXCEPT IN U.S. PLAINTIFF CASES) 99999	COUNTY OF RESIDENCE OF FIRST LISTED DEFENDANT (IN U.S. PLAINTIFF CASES ONLY) NOTE: IN LAND CONDEMNATION CASES, USE THE LOCATION OF THE TRACT OF LAND INVOLVED
(c) ATTORNEYS (FIRM NAME, ADDRESS, AND TELEPHONE NUMBER) Christopher J. Kelly Mayer Brown LLP 1909 K St., N.W. Washington, DC 20006 202-263-3000	ATTORNEYS (IF KNOWN)

II. BASIS OF JURISDICTION

(PLACE AN x IN ONE BOX ONLY)

- ○ 1 U.S. Government Plaintiff
- ○ 3 Federal Question (U.S. Government Not a Party)
- ◉ 2 U.S. Government Defendant
- ○ 4 Diversity (Indicate Citizenship of Parties in item III)

III CITIZENSHIP OF PRINCIPAL PARTIES (PLACE AN x IN ONE BOX FOR PLAINTIFF AND ONE BOX FOR DEFENDANT) FOR DIVERSITY CASES ONLY!

	PTF	DFT		PTF	DFT
Citizen of this State	○ 1	○ 1	Incorporated or Principal Place of Business in This State	○ 4	○ 4
Citizen of Another State	○ 2	○ 2	Incorporated and Principal Place of Business in Another State	○ 5	○ 5
Citizen or Subject of a Foreign Country	○ 3	○ 3	Foreign Nation	○ 6	○ 6

IV. CASE ASSIGNMENT AND NATURE OF SUIT

(Place a X in one category, A-N, that best represents your cause of action and one in a corresponding Nature of Suit)

○ A. *Antitrust*

- ☐ 410 Antitrust

○ B. *Personal Injury/ Malpractice*

- ☐ 310 Airplane
- ☐ 315 Airplane Product Liability
- ☐ 320 Assault, Libel & Slander
- ☐ 330 Federal Employers Liability
- ☐ 340 Marine
- ☐ 345 Marine Product Liability
- ☐ 350 Motor Vehicle
- ☐ 355 Motor Vehicle Product Liability
- ☐ 360 Other Personal Injury
- ☐ 362 Medical Malpractice
- ☐ 365 Product Liability
- ☐ 368 Asbestos Product Liability

○ C. *Administrative Agency Review*

- ☐ 151 Medicare Act

Social Security:
- ☐ 861 HIA ((1395ff)
- ☐ 862 Black Lung (923)
- ☐ 863 DIWC/DIWW (405(g)
- ☐ 864 SSID Title XVI
- ☐ 865 RSI (405(g)

Other Statutes
- ☐ 891 Agricultural Acts
- ☐ 892 Economic Stabilization Act
- ☐ 893 Environmental Matters
- ☐ 894 Energy Allocation Act
- ☒ 890 Other Statutory Actions (If Administrative Agency is Involved)

○ D. *Temporary Restraining Order/Preliminary Injunction*

Any nature of suit from any category may be selected for this category of case assignment.

(If Antitrust, then A governs)

○ E. *General Civil (Other)* OR ○ F. *Pro Se General Civil*

Real Property
- ☐ 210 Land Condemnation
- ☐ 220 Foreclosure
- ☐ 230 Rent, Lease & Ejectment
- ☐ 240 Torts to Land
- ☐ 245 Tort Product Liability
- ☐ 290 All Other Real Property

Personal Property
- ☐ 370 Other Fraud
- ☐ 371 Truth in Lending
- ☐ 380 Other Personal Property Damage
- ☐ 385 Property Damage Product Liability

Bankruptcy
- ☐ 422 Appeal 28 USC 158
- ☐ 423 Withdrawal 28 USC 157

Prisoner Petitions
- ☐ 535 Death Penalty
- ☐ 540 Mandamus & Other
- ☐ 550 Civil Rights
- ☐ 555 Prison Condition

Property Rights
- ☐ 820 Copyrights
- ☐ 830 Patent
- ☐ 840 Trademark

Federal Tax Suits
- ☐ 870 Taxes (US plaintiff or defendant
- ☐ 871 IRS-Third Party 26 USC 7609

Forfeiture/Penalty
- ☐ 610 Agriculture
- ☐ 620 Other Food &Drug
- ☐ 625 Drug Related Seizure of Property 21 USC 881
- ☐ 630 Liquor Laws
- ☐ 640 RR & Truck
- ☐ 650 Airline Regs
- ☐ 660 Occupational Safety/Health
- ☐ 690 Other

Other Statutes
- ☐ 400 State Reapportionment
- ☐ 430 Banks & Banking
- ☐ 450 Commerce/ICC Rates/etc.
- ☐ 460 Deportation
- ☐ 470 Racketeer Influenced & Corrupt Organizations
- ☐ 480 Consumer Credit
- ☐ 490 Cable/Satellite TV
- ☐ 810 Selective Service
- ☐ 850 Securities/Commodities/ Exchange
- ☐ 875 Customer Challenge 12 USC 3410
- ☐ 900 Appeal of fee determination under equal access to Justice
- ☐ 950 Constitutionality of State Statutes
- ☐ 890 Other Statutory Actions (if not administrative agency review or Privacy Act

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

SOLVAY PHARMACEUTICALS GmbH
Hans-Boeckler Allee 20, 30173 Hannover, Germany,

Plaintiff,

v.

HON. JON W. DUDAS,
Under Secretary of Commerce for Intellectual Property and Director of the United States, Patent and Trademark Office,
Office of General Counsel, United States Patent and Trademark Office, P.O. Box 15667, Arlington, VA 22215,
10B20, Madison Building East, 600 Dulany Street, Alexandria, VA 22314,

Defendant.

Civil Action No. _____

COMPLAINT

Plaintiff Solvay Pharmaceuticals GmbH ("Solvay"), for its complaint against the Honorable Jon W. Dudas, states as follows:

NATURE OF THE ACTION

1. This is an action by Solvay, the applicant and owner of United States Patent No. 7,381,729 ("the '729 patent") for review of the determination by Defendant, pursuant to 35 U.S.C. § 154(b)(3)(B), of the patent term adjustment of the '729 patent. Plaintiff seeks a judgment, pursuant to 35 U.S.C. § 154(b)(4)(A), that the patent term adjustment for the '729 patent be changed from 534 days to 633 days.

2. This action arises under 35 U.S.C. § 154(b)(4)(A) and the Administrative Procedure Act, 5 U.S.C. §§ 701-706.

THE PARTIES

3. Plaintiff Solvay is a company organized under the laws of the Federal Republic of Germany, with its principal place of business at Hans-Boeckler Allee 20, Hannover, Germany.

4. Defendant Jon W. Dudas is the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office ("PTO"), acting in his official capacity. The Director is the head of the PTO and is responsible for superintending or performing all duties required by law with respect to the granting and issuing of patents, and is designated by statute as the official responsible for determining the period of patent term adjustments under 35 U.S.C. § 154(b)(3)(B).

JURISDICTION AND VENUE

5. This Court has jurisdiction to hear this action and is authorized to issue the relief sought pursuant to 28 U.S.C. §§ 1331, 1338(a) and 1361, 35 U.S.C. § 154(b)(4)(A), and 5 U.S.C. §§ 701-706.

6. Venue is proper in this district by virtue of 35 U.S.C. § 154(b)(4)(A).

7. This Complaint is being timely filed in accordance with 35 U.S.C. § 154(b)(4)(A).

FACTS

8. Plaintiff Solvay is the assignee of all right, title and interest in the '729 patent, as evidenced by records on deposit with the PTO, and is the real party in interest in this case.

9. Axel Pahl, Timo Heinrich, Emil Finner, Bernd-Martin Luitjens, Jan Zorgdrager, and Pieter C. Verveer are the inventors of patent application number 10/828,650 ("the '650 application").

10. The '650 application was filed on April 21, 2004, and issued as the '729 patent on June 3, 2008. The '729 patent is attached as Exhibit A.

11. On October 11, 2006, the PTO mailed the first notification under 35 U.S.C. § 132 ("the First Office Action") as to the '650 application.

12. On July 30, 2007, Plaintiff filed with the PTO a first and only request for continued examination ("the RCE") of the '650 application.

13. On September 10, 2007, the PTO mailed a Notice of Allowance and Fees Due for the '650 application. Included in the Notice of Allowance and Fees Due was a Determination of Patent Term Adjustment in which the PTO indicated that the patent term adjustment to date for the '650 application was 477 days.

14. On December 7, 2007, Plaintiff paid the issue fee for the '650 application, thereby satisfying all outstanding requirements for issuance of a patent therefrom.

15. On December 7, 2007, Plaintiff also filed with the PTO an Application for Patent Term Adjustment requesting that the PTO change its patent term adjustment to include an additional 100 days. On March 31, 2008, the PTO held in abeyance a decision on Plaintiff's Application for Patent Term Adjustment pending the issuance of the '729 patent.

16. The '729 patent issued on June 3, 2008, indicating a patent term adjustment of 534 days, evidently reflecting the additional 57-day delay in issuing the patent beyond four months after the date on which Solvay had paid the issue fee and all outstanding requirements were satisfied, pursuant to 35 U.S.C. § 154(b)(1)(A)(iv).

17. On June 25, 2008, Plaintiff filed a Request for Reconsideration of the December 7, 2007 Application for Patent Term Adjustment, renewing its request that the PTO change its

patent term adjustment calculation for the '729 patent. The PTO dismissed Plaintiff's Request for Reconsideration on September 30, 2008.

18. 35 U.S.C. § 154(b) requires that patent terms be adjusted to compensate for failures of the PTO to take certain actions on patent applications within designated time limits. 35 U.S.C. § 154(b)(3) requires the Director of the PTO to determine the patent term adjustment for each patent.

19. In calculating the patent term adjustment, the Director must take into account PTO delays under 35 U.S.C. § 154(b)(1), any overlapping periods in the PTO delays under 35 U.S.C. § 154(b)(2)(A), and any applicant delays under 35 U.S.C. § 154(b)(2)(C).

20. Under 35 U.S.C. § 154(b)(4)(A), "[a]n applicant dissatisfied with a determination made by the Director under paragraph (3) shall have remedy by a civil action against the Director filed in the United States District Court for the District of Columbia within 180 days after the grant of the patent. Chapter 7 of title 5 shall apply to such action."

CLAIM FOR RELIEF

21. The allegations of paragraphs 1-20 are incorporated in this claim for relief as if fully set forth herein.

22. The currently challenged patent term adjustment for the '729 patent, as determined by the Defendant under 35 U.S.C. § 154(b), and listed on the face of the '729 patent, is 534 days. (*See* Ex. A at p.1). This determination of the 534-day patent term adjustment is in error in that it fails to include an adjustment, as required by 35 U.S.C. § 154(b)(1)(B), for the time from three years after the filing date of the '650 application to the date the patent issued, not including the period of time following Plaintiff's request for continued examination (*i.e.*, not including the period of time between the filing of the RCE and the grant of the '729 patent). The

number of days in the period from April 21, 2007 (three years after the filing date of the '650 application) until July 29, 2007 (the day before the filing of the RCE) is 99 days. Therefore, the correct patent term adjustment for the '729 patent, including both the 534-day period determined by the PTO and this 99-day additional adjustment under 35 U.S.C. § 154(b)(1)(B), is 633 days.

23. Under 35 U.S.C. § 154(b)(1)(A), Plaintiff is entitled to an adjustment of the term of the '729 patent of 534 days, the number of days attributable to PTO examination delay ("A Delay"). The A Delay period consists of the following:

a. A period of 477 days pursuant to 35 U.S.C. § 154(b)(1)(A)(i) due to the PTO's failure to mail an action under 35 U.S.C. § 132 not later than 14 months from the actual filing date of the application. This period consists of the length of time from June 21, 2005 (14 months after the filing date of the '650 application) to October 11, 2006 (the mailing date of the First Office Action).

b. A period of 57 days pursuant to 35 U.S.C. § 154(b)(1)(A)(iv) due to the PTO's failure to issue the '729 patent within four months after the date the issue fee was paid. This period consists of the length of time from April 7, 2008 (four months after the date the issue fee was paid) to June 3, 2008 (the date the '729 patent issued).

24. Under 35 U.S.C. § 154(b)(1)(B), Plaintiff is entitled to an additional adjustment of the term of the '729 patent of 99 days, the number of days attributable to the PTO's "failure . . . to issue a patent within 3 years after the actual filing date of the ['650] application," but not including "any time consumed by continued examination of the application requested by the applicant under section 132 (b)" ("B Delay"). The B Delay period therefore consists of the period commencing April 21, 2007 (three years after the filing date of the '650 application) until

the issue date of the '729 patent, excluding the period between July 29, 2007 (the day before the filing date of the RCE) and June 3, 2008 (the issue date of the '729 patent).

25. 35 U.S.C. § 154(b)(2)(A) states that "to the extent . . . periods of delay attributable to grounds specified in paragraph [154(b)(1)] overlap, the period of any adjustment granted under this subsection shall not exceed the actual number of days the issuance of the patent was delayed." For the '729 patent, none of the A Delay period overlaps with the B Delay period. Therefore, there is no period of overlap to be excluded from the determination of patent term adjustment for the '729 patent under 35 U.S.C. § 154(b)(2)(A).

26. Thus the total period of PTO delay is 633 days, the sum of the period of A Delay (534 days) and the period of B Delay (99 days).

27. As determined by the Defendant, there was no period of applicant delay under 35 U.S.C. § 154(b)(2)(C) that would reduce the period of PTO delay.

28. Accordingly, the correct patent term adjustment for the '729 patent under 35 U.S.C. §§ 154(b)(1) and (2) is 633 days.

29. Defendant's determination that the period of the patent term adjustment for the '729 patent is only 534 days, his failure to include in the patent term adjustment the 99 days required by 35 U.S.C. § 154(b)(1)(B) and his refusal to reconsider the patent term adjustment of the '729 patent are arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law and in excess of statutory jurisdiction, authority or limitation.

30. Moreover, Defendant's determination that the period of the patent term adjustment for the '729 patent is only 534 days is in conflict with this Court's judgment in Wyeth v. Dudas, Civ. Action No. 1:07-cv-01492-JR, 2008 WL 4445642 (D.D.C. Sept. 30, 2008),

which explains the proper method for calculating patent term adjustments under 35 U.S.C. § 154(b).

WHEREFORE, Plaintiff respectfully prays that this Court:

A. Issue an Order changing the period of patent term adjustment for the '729 patent from 534 days to 633 days, and requiring Defendant to alter the term of the '729 patent to reflect the 633-day patent term adjustment; and

B. Grant such other and further relief as the nature of the case may admit or require and as may be just and equitable.

Respectfully submitted,

Dated: November 26, 2008

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Attorneys for Plaintiff Solvay Pharmaceuticals GmbH

Solvay Pharmaceuticals GmbH v. Dudas

No. _____

EXHIBIT A TO COMPLAINT

(12) **United States Patent**
Pahl et al.

(10) **Patent No.: US 7,381,729 B2**
(45) **Date of Patent: Jun. 3, 2008**

(54) **4-(4-TRANS-HYDROXYCYCLOHEXYL)-AMINO-2-PHENYL-7H-PYRROLO [2,3D] PYRIMIDINE HYDROGEN MESYLATE, ITS POLYMORPHIC FORMS, AND METHODS FOR MAKING SAME**

(75) Inventors: **Axel Pahl**, Lindwedel (DE); **Timo Heinrich**, Gross-Umstadt (DE); **Emil Finner**, Isernhagen (DE); **Bernd-Martin Luitjens**, Hannover (DE); **Jan Zorgdrager**, Zaandam (NL); **Pieter C. Verveer**, Utrecht (NL)

(73) Assignee: **Solvay Pharmaceuticals B.V.**, Weesp (NL)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 534 days.

(21) Appl. No.: **10/828,650**

(22) Filed: **Apr. 21, 2004**

(65) **Prior Publication Data**

US 2004/0248912 A1 Dec. 9, 2004

Related U.S. Application Data

(60) Provisional application No. 60/464,422, filed on Apr. 22, 2003.

(51) **Int. Cl.**

C07D 487/04	(2006.01)
A61K 31/519	(2006.01)
A61P 9/04	(2006.01)
A61P 13/12	(2006.01)
A61P 9/12	(2006.01)

(52) **U.S. Cl.** **514/265.1**; 544/280

(58) **Field of Classification Search** 544/280; 514/265.1

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

6,878,716 B1 * 4/2005 Castelhano et al. 514/265.1

FOREIGN PATENT DOCUMENTS

WO	1999/62518	12/1999
WO	2004/094428	11/2004

OTHER PUBLICATIONS

Engel et al. (Inter. J. Pharm., 2000, 198(2). 239-247.*
Bernstein et al., Concomitant Polymorphs, Angew. Chem. Int. Ed., vol. 38 (1999) p. 3440-3461.
Threlfall, Analysis of Organic Polymorphs: A Review, Analyst, vol. 120 (Oct. 1995) p. 2435-2460.
International Preliminary Report on Patentability, PCT/EP2004/050573 (Jul. 14, 2005).
Written Opinion of the International Searching Authority, PCT/EP2004/050573 (Received Jul. 14, 2004).

* cited by examiner

Primary Examiner—Brenda L. Coleman
Assistant Examiner—Susanna Moore
(74) *Attorney, Agent, or Firm*—Mayer Brown LLP

(57) **ABSTRACT**

The present invention relates to the novel compound 4-(4-trans-hydroxycyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d] pyrimidine hydrogen mesylate, the polymorphic α and β forms thereof, and a method for the production of said compounds.

17 Claims, 6 Drawing Sheets

Figure 1: XRPD pattern of polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate

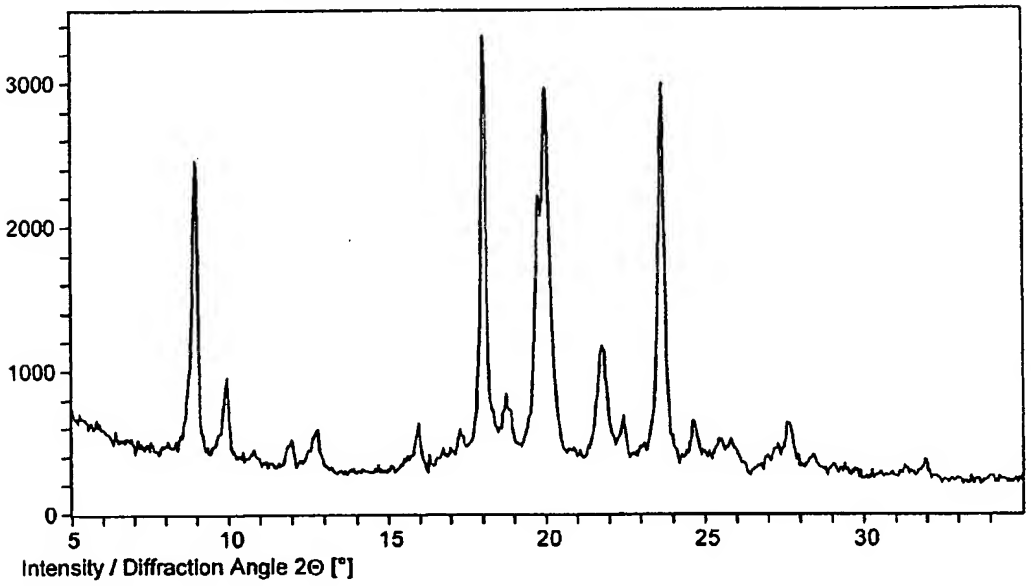


Figure 2: IR (ATR) spectrum of form polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate

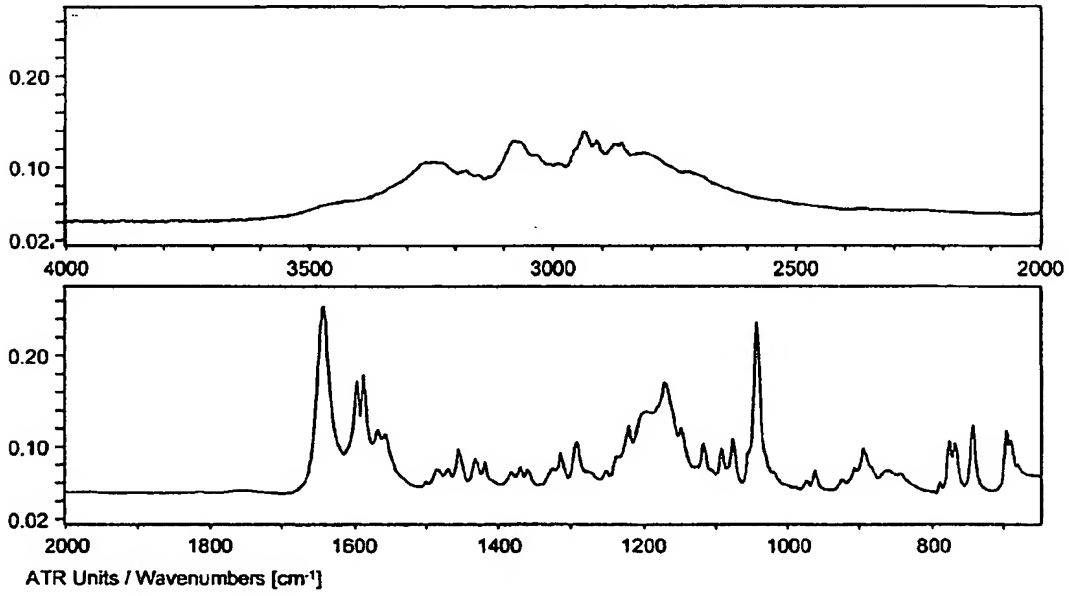


Figure 3: DSC trace of form polymorphic form α of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate

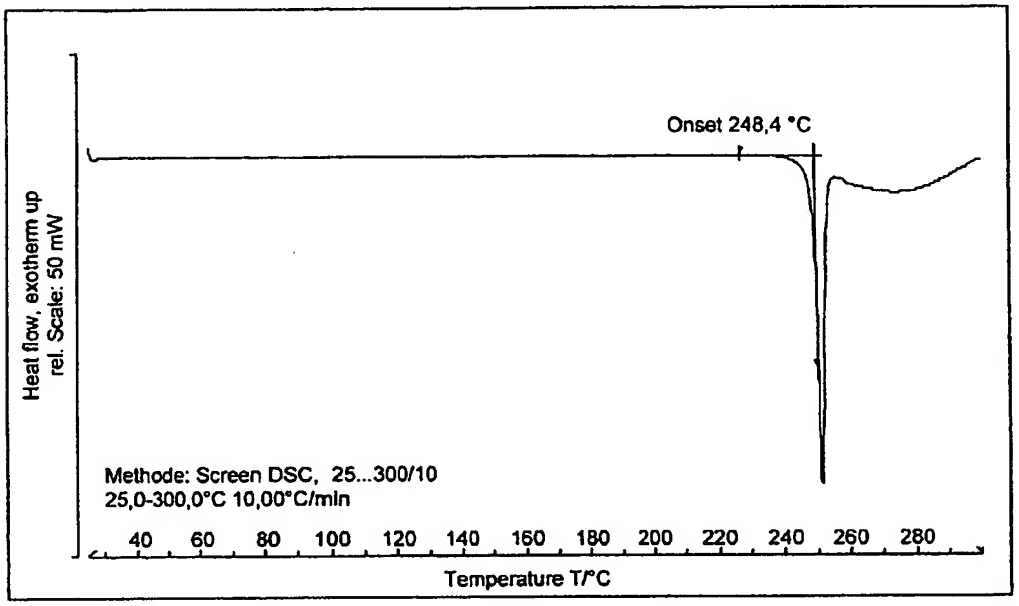


Figure 4: XRPD pattern of polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate

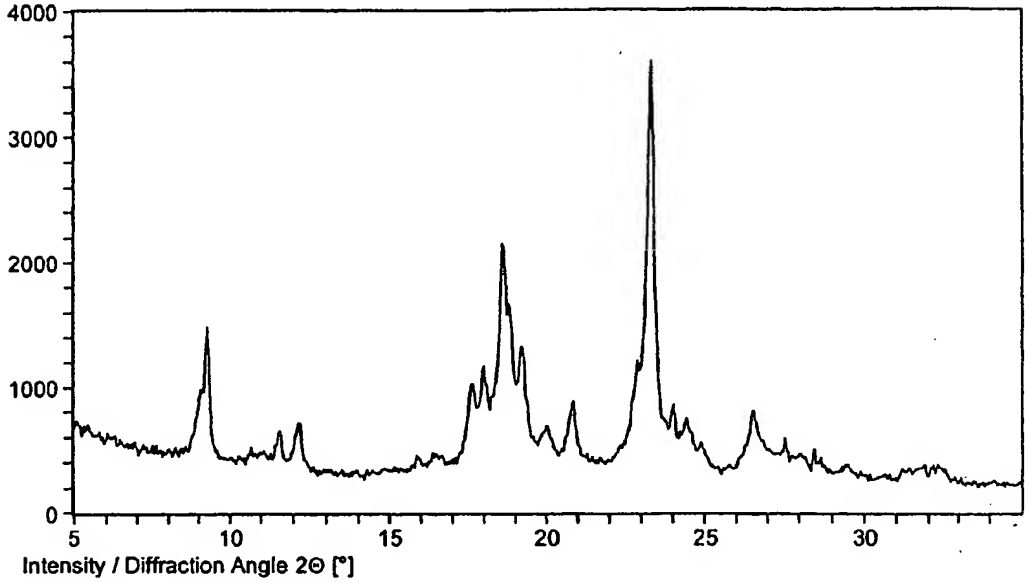


Figure 5: IR (ATR) spectrum of polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate

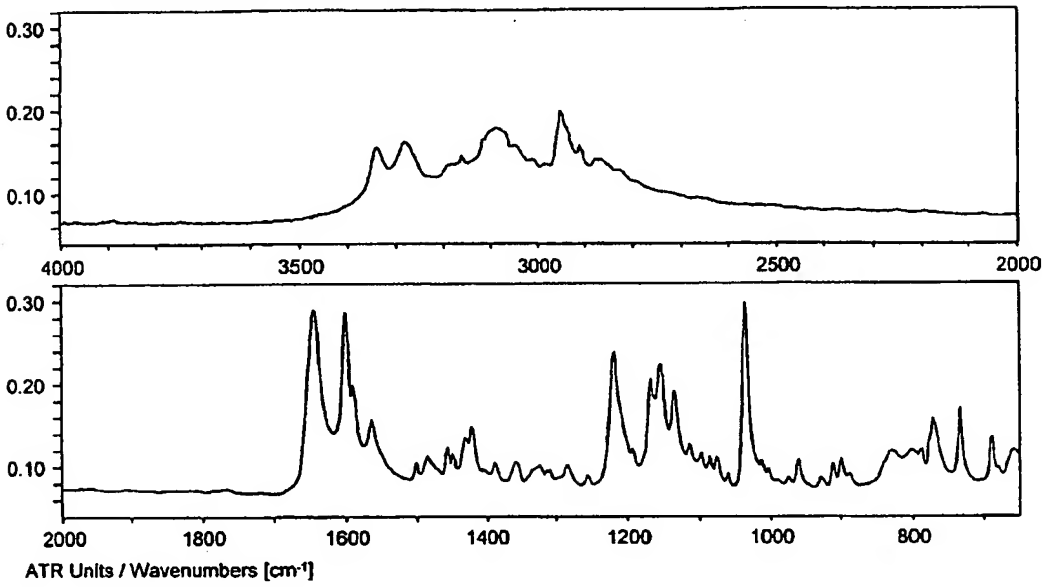
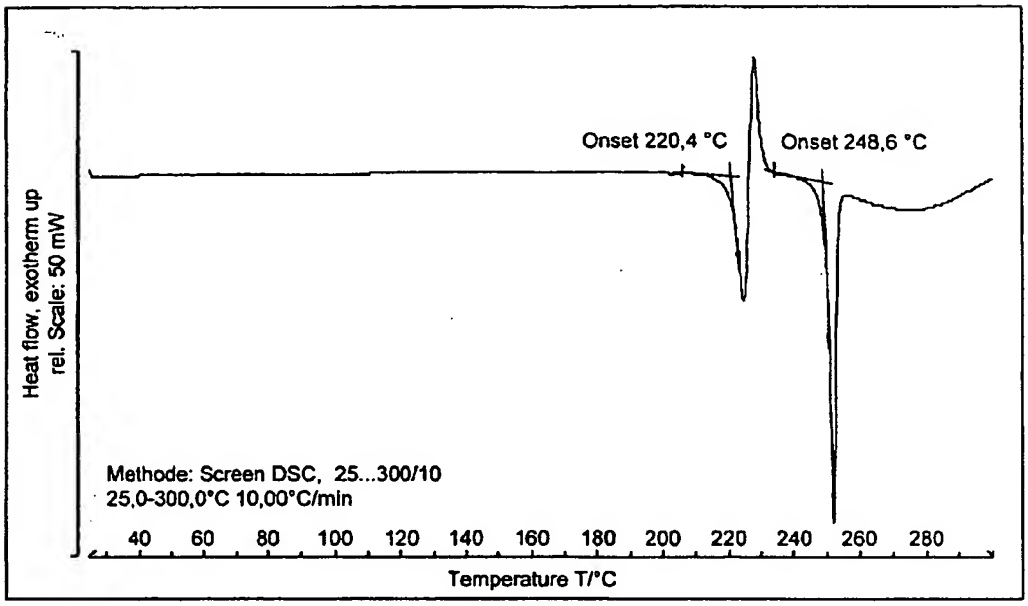


Figure 6: DSC trace of polymorphic form β of 4-(4-*trans*-hydroxy-cyclohexyl)amino-2-phenyl-7*H*-pyrrolo[2,3d]pyrimidine mesylate



4-(4-TRANS-HYDROXYCYCLOHEXYL)-AMINO-2-PHENYL-7H-PYRROLO [2,3D] PYRIMIDINE HYDROGEN MESYLATE, ITS POLYMORPHIC FORMS, AND METHODS FOR MAKING SAME

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Appl. No. 60/464,422 filed Apr. 22, 2003, and European Patent Appl. No. 03101093.7, filed Apr. 22, 2003, which are incorporated herein in their entirety.

FIELD OF THE INVENTION

The present invention relates to the novel compound 4-(4-trans-hydroxycyclohexyl) amino-2-phenyl-7H-pyrrolo [2,3d]pyrimidine hydrogen mesylate, different polymorphic forms thereof, and a method for the production of said compounds.

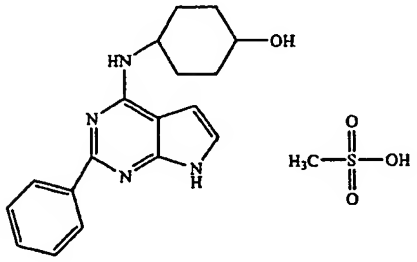
BACKGROUND OF THE INVENTION

4-(4-trans-hydroxycyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine is disclosed in WO 99/62518 (compound 18 on page 53) and is a selective Adenosine-1 Receptor agonist that may be used in the treatment of essential hypertension, congestive heart failure, and renal failure. During further development of said compound in the above-mentioned indications, it appeared that the compound as disclosed in WO 99/62518 has the serious drawback of a low solubility in gastrointestinal fluids.

SUMMARY OF THE INVENTION

The present invention provides pharmaceutical compositions comprising a salt of 4-(4-trans-hydroxy-cyclohexyl) amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine. It is an object of the present invention to provide a salt of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine that is a crystalline, homogeneous, and stable product that has superior solubility properties.

This object can be achieved, according to the present invention, by the hydrogen mesylate salt of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]-pyrimidine. In the framework of the present application, this compound is further referred to as 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]-pyrimidine mesylate. The compound has the following structure:



In one embodiment, the compositions of the invention are a pharmaceutical dosage form (e.g., parenteral solution, tablet, powder, capsule, gel, cream, ointment, transdermal patch, inhalant solution or suspension, or oral solution or suspension.)

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a line graph illustrating the X-ray powder diffraction ("XRPD") pattern of polymorphic form αof 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo [2,3d]pyrimidine mesylate.

FIG. 2 is a line graph illustrating the infrared ("IR") spectrum, recorded in attenuated total reflectance ("ATR"), of polymorphic form αof 4-(4-trans-hydroxy-cyclohexyl) amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate.

FIG. 3 is a line graph illustrating the differential scanning calorimeter ("DSC") trace of polymorphic form αof 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2, 3d]pyrimidine mesylate.

FIG. 4 is a line graph illustrating the XRPD pattern of polymorphic form β of 4-(4-trans-hydroxy-cyclohexyl) amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate.

FIG. 5 is a line graph illustrating the IR spectrum. recorded in ATR, of polymorphic form β of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate.

FIG. 6 is a line graph illustrating the DSC trace of polymorphic form β of 4-(4-trans-hydroxy-cyclohexyl) amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate.

DETAILED DESCRIPTION OF THE INVENTION

The composition of the present invention broadly relates to the salts of 4-(4-trans-hydroxycyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine. In contrast to the camphorsulfonate, mono-ethanedisulfonate, mono-isethionate, phosphate and sulfate salts, the mesylate salt is highly soluble in water. Further, 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]-pyrimidine mesylate appears to be very stable at ambient conditions.

Crystalline 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate was found to exist in two polymorphic forms, further indicated as polymorphic forms α and β. Both polymorphic forms have improved solubility, although form αhas a better solubility than form β. Form α is metastable with respect to form β. Form β is the currently known stable form.

Substantially pure form α can be obtained in a laboratory setting by adding a solution of methane sulfonic acid in methanol to a suspension of 4-(4-trans-hydroxy-cyclohexyl) amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine in methanol, followed by the addition of isopropanol. Substantially pure form β can be obtained by adding a solution of methane sulfonic acid in ethanol to a solution of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine in ethanol, followed by the addition of water and stirring. The pure form β can also be obtained by stirring samples of pure form α in a mixture of ethanol and water. The term "substantially pure" means a purity of at least about 75%, or about 80%, or about 85%, or about 90%, or about 95%, or about 97%, or about 99%, or about 100% weight-to-weight of the composition.

The polymorphic form α of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate, according to the present invention, is defined by the following physicochemical characteristics:

(i) An XRPD pattern having characteristic reflexes (expressed in degrees of diffraction angle 2θ) at approximately: 9.0, 10.0, 12.8, 15.9, 18.1, 18.8, 19.8, 20.1, 21.8, 23.7. Diffraction angles are indicated as mean values

(±0.1°) of six independent measurements. The complete XRPD pattern for the polymorphic form α is shown in FIG. 1.

(ii) An IR spectrum, recorded in ATR, having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3246, 1644, 1455, 1381, 1368, 1292, 1117, 1092, 1042, 743. The complete IR spectrum for the polymorphic form α is shown in FIG. 2.

(iii) A melting point at approximately 248° C. (onset temperature) measured by DSC. The complete DSC trace for the polymorphic form α is shown in FIG. 3.

The polymorphic form β of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate, according to the present invention, is defined by the following physicochemical characteristics:

(i) An XRPD pattern having characteristic reflexes (expressed in degrees of diffraction angle 2θ) at approximately: 9.3, 11.6, 12.2, 17.6, 18.0, 18.6, 19.3, 20.8, 23.4, 26.5. Diffraction angles are indicated as mean values (±0.1°) of four independent measurements. The complete XRPD pattern for the polymorphic form β is shown in FIG. 4.

(ii) An IR spectrum, recorded in ATR, having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3338, 3279, 1602, 1564, 1389, 1219, 1154, 1134, 1034, 732. The complete IR spectrum for the polymorphic form β is shown in FIG. 5.

(iii) A melting point at approximately 220° C. (onset temperature) measured by DSC. The complete DSC trace for the polymorphic form β is shown in FIG. 6.

4-(4-trans-hydroxycyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine is known to be useful in treating and/or preventing essential hypertension, congestive heart failure, and renal failure in mammals. 4-(4-trans-hydroxycyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine can also be administered as its hydrogen mesylate salt. Preferably, compositions of the present invention are administered in a therapeutically effective amount.

The term, "therapeutically effective amount," as used herein refers to an amount of compound that is sufficient to elicit the required or desired therapeutic and/or prophylactic response, as the particular treatment context may require. It will be understood that a therapeutically effective amount of a drug for a subject is dependent inter alia on the body weight of the subject, the age of a subject, the severity of the subject's symptoms, the subject's response to the compound, and the route of administration.

In one embodiment, the therapeutically effective amount of the compound for a subject is a dosage in the range of from about 0.01 to about 200 mg per kilogram body weight per day. In another embodiment, the therapeutically effective amount of the compound for a subject is a dosage in the range of from about 0.1 to about 100 mg per kilogram body weight per day. Such amounts maybe administered in single or divided daily doses.

A "subject" herein to which the compositions of the present invention can be administered includes a human subject of either sex and of any age, and also includes any nonhuman animal, particularly a domestic or companion animal, illustratively a cat, dog, monkey, lemur, or a horse.

The "route of administration" comprises administering the compositions of the present invention either orally, transdermally, or parenterally, and any combination thereof.

In a preferred embodiment, a therapeutically effective amount of the compound is administered parenterally to treat acute heart failure.

Compositions according to the present invention intended for oral, transdermal and/or parenteral administration may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions. Such compositions may comprise one or more materials selected from the group consisting of coloring agents, flavoring agents, sweetening agents, and preservatives.

Formulations for oral use may, among other things, be tablets that contain the active ingredient in admixture with pharmaceutically acceptable excipients, such as binding agents (e.g., starch, acacia, gelatin), lubricating agents (e.g., stearic acid, magnesium stearate, talc), granulating and disintegrating agents (e.g., corn starch, alginic acid), and inert diluents (e.g., calcium phosphate, sodium phosphate, calcium carbonate, sodium carbonate, lactose). Moreover, formulations for oral use may also be soft gelatin capsules wherein the active ingredient is mixed with water or an oily medium such as liquid paraffin, peanut oil, or olive oil or hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent such as kaolin, calcium carbonate, or calcium phosphate.

The following examples are only intended to further illustrate the invention in more detail, and therefore, these examples are not deemed to restrict the scope of the invention in any way.

EXAMPLE 1

Preparation of Polymorphic Form α of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine Mesylate

701 g of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine prepared according to the method described in WO 99/62518 are suspended in 4.5 L methanol. A solution of 240 g methane sulfonic acid in 750 mL methanol is added under stirring, leading to a clear solution. The mixture is concentrated to 1900 g, then 5.5 L isopropanol are added at room temperature and the mixture is stirred for 44 h. The product is filtrated, washed four times with 0.5 L isopropanol each, and dried for 40 h at 95° C. in a vacuum drying oven to give 780 g of the title compound as crystalline modification α.

EXAMPLE 2

Preparation of Polymorphic Form α of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine Mesylate

2.00 g of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine (=6.50 mmol) was dissolved in 70 mL of acetone at reflux temperature. Under stirring at reflux temperature there was added a solution of 0.62 g of methanesulfonic acid (=6.50 mmol) in 7 mL of acetone. The reaction mixture was stirred at reflux temperature for 10 minutes. After this the reaction mixture was cooled to room temperature by removing the heating mantle. The resulting suspension was stirred for 1 hour at 2° C. The product was collected by filtration, washed twice with 5 mL of acetone, and dried under vacuo at 50° C. for 24 hours. This gave 2.49 g of crystalline modification α (=95% c/c).

The polymorphic form α was also obtained from the solvents, acetonitrile and 2-butanone, according to a similar procedure.

EXAMPLE 3

Preparation of Polymorphic Form β of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine Mesylate

2.00 g of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine (=6.50 mmol) was dissolved in a mixture of 45 mL of acetone and 5 mL of water at reflux temperature. Under stirring at reflux temperature there was added a solution of 0.62 g of methanesulfonic acid (=6.50 mmol) in 5 mL of acetone. The reaction mixture was stirred at reflux temperature for 10 minutes. The reaction mixture was then cooled to room temperature by removing the heating mantle. The resulting suspension was stirred for 45 hours at room temperature. The product was collected by filtration, washed twice with 5 mL of acetone and dried under vacuo at 50° C. for 24 hours. This gave 2.26 g of crystalline modification β (=86%).

The polymorphic form β was also obtained from the solvent mixtures acetonitrile/water and 2-butanone/water, according to a similar procedure.

EXAMPLE 4

Rearrangement of Polymorphic Form α of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine Mesylate into its Polymorphic Form β

5302 g of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine mesylate modification a was stirred in 20 L of ethanol and 2 L of water for 5 days at ambient temperature. The product was filtrated and dried at 70° C. for 40 h in a circulating air drier to give 3444 g of the title compound as crystalline modification β.

EXAMPLE 5

Analytical Methods

XRPD patterns were measured on a diffractometer using monochromatic CuKα radiation (tube voltage 40 kV, tube current 40 mA). IR spectra were recorded on a Fourier transform IR spectrometer in ATR (silicon crystal) with a spectral resolution of 2 cm^{-1} using a deuterated triglycine sulfate detector.

Melting points were determined on a DSC apparatus as onset temperatures of the melting endotherm using 40 μL aluminum crucibles with a pierced lid. Temperature program: heating from 25° C. up to 300° C. with 10 K min^{-1}. N_2 atmosphere at a flow of 60 mL min^{-1}.

Solubility measurements were carried out with the shake flask method according to the OECD guideline at 25° C. (OECD Guideline for testing of chemicals, No. 105 (issued May 12, 1981)).

EXAMPLE 6

Solubility of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine and its Mesylates Polymorphic Form α and β

Measurement of the solubility of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine and its mesylates polymorphic form α and β in purified water gave the following results.

Compound	Solubility in mg/L
Base	0.0059
Polymorph α	77
Polymorph β	18.5

The contents of all cited references throughout this application are hereby expressly incorporated by reference. The practice of the present invention will employ, unless otherwise indicated, conventional techniques of pharmacology and pharmaceutics, which are within the skill of the art.

Although the invention has been described with respect to specific embodiments and examples, it should be appreciated that other embodiments utilizing the concept of the present invention are possible without departing from the scope of the invention. The present invention is defined by the claimed elements, and any and all modifications, variations, or equivalents that fall within the true spirit and scope of the underlying principles.

The invention claimed is:

1. The compound 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate.

2. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (α) exhibiting an X-ray powder diffraction pattern having characteristic reflexes (expressed in degrees of diffraction angle 2θ) at approximately: 9.0, 10.0, 12.8, 15.9, 18.1, 18.8, 19.8, 20.1, 21.8, 23.7.

3. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (α), characterized by an X-ray powder diffraction pattern shown in FIG. 1.

4. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (α), exhibiting an infrared spectrum recorded in attenuated total reflectance having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3246, 1644, 1455, 1381, 1368, 1292, 1117, 1092, 1042, 743.

5. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (α), characterized by a complete infrared spectrum shown in FIG. 2.

6. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (α), exhibiting a melting point at approximately 248° C.

7. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (α), characterized by a complete differential scanning calorimeter trace shown in FIG. 3.

8. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (β), exhibiting an X-ray powder diffraction pattern having characteristic reflexes (expressed in degrees of diffraction angle 2θ) at approximately: 9.3, 11.6, 12.2, 17.6, 18.0, 18.6, 19.3, 20.8, 23.4, 26.5.

9. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (β), characterized by an X-ray powder diffraction pattern shown in FIG. 4.

10. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (β), exhibiting an infrared spectrum recorded in attenuated total reflectance having characteristic absorption bands expressed in reciprocal centimeters at approximately: 3338, 3279, 1602, 1564, 1389, 1219, 1154, 1134, 1034, 732.

11. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (β), characterized by a complete infrared spectrum shown in FIG. 5.

12. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (β), exhibiting a melting point at approximately 220° C.

13. The compound of claim 1, wherein the 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate is in a polymorphic form (β), characterized by a complete differential scanning calorimeter trace shown in FIG. 6.

14. A composition comprising at least one compound from any one of claims 1-13 and a pharmaceutically acceptable carrier.

15. The composition of claim 14, comprising an effective amount of 4-(4-trans-hydroxy-cyclohexyl)amino-2-phenyl-7H-pyrrolo[2,3d]pyrimidine hydrogen mesylate.

16. The composition of claim 15, in a parenteral dosage form.

17. A method for the treatment of a condition selected from the group consisting of essential hypertension, congestive heart failure and renal failure, comprising administering an effective amount of at least one compound from any one of claims 1-13.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 7,381,729 B2
APPLICATION NO. : 10/828650
DATED : June 3, 2008
INVENTOR(S) : Axel Pahl et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title page of the patent Item [73] delete the following Assignee:

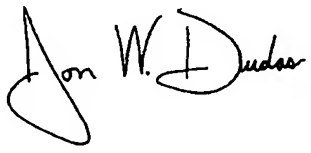
Solvay Pharmaceuticals B.V., Weesp (NL)

and insert the following Assignee:

Solvay Pharmaceuticals GmbH, Hannover (DE)

Signed and Sealed this

Fourth Day of November, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office